NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Midostaurin for untreated acute myeloid leukaemia [ID894]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Novartis (company)
   - National Clinical Research Institute, Association of Cancer Physicians and Royal College of Physicians (joint response) – endorsed by clinical experts Dr Steven Knapper and Dr Mike Dennis
   - Leukaemia CARE

   The Department of Health submitted a "No Comment" response

   There were no comments received from patient or clinical experts

   There were no comments received through the NICE website

3. **Appendix of new evidence** – prepared by Novartis

4. **Evidence Review Group critique of company ACD response and new evidence –** prepared by CRD and CHE Technology Assessment Group, University of York

5. **Company updated value proposition and new analyses** – submitted by Novartis

6. **Evidence Review Group critique of company new submission and analyses –** prepared by CRD and CHE Technology Assessment Group, University of York

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Midostaurin for untreated acute myeloid leukaemia
Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Novartis Pharmaceuticals	1. Factual inaccuracies In the slides presented to the committee, the ERG explained the impact on the ICER resulting from each change to the model, both individually and cumulatively. We believe that these analyses were mislabelled by the ERG, in that the change in the ICER reported did not correspond to the correct change in the model. Whilst this does not affect the ERG base-case, we believe that the mislabelling could have misled the committee on drivers of the ICER. We believe the correct labelling of the table shown in slide 19 of the ACM papers to be that shown in the appendix, table 1.	Thank you for your comment. There was a factual inaccuracy in the summary table on slide 19 of the slides. However, the figures were correct in the other slides, and in the committee papers. The factual inaccuracy has been corrected in the public committee slides and pre-meeting briefing on the NICE website.
2	Company	Novartis Pharmaceuticals	2. Additional evidence to support End of Life Considering the evidence, the committee felt that the survival in people newly diagnosed with FLT3 mutation-positive AML was more than 24 months, based on a study conducted by Knapper et al (2017) and the median OS of 26 months from the RATIFY trial. Whilst the exact reference of the Knapper study (2017) considered by the committee is not included in the ACD, we believe that the committee referred to the following study: Knapper et al. Blood. 2017 Mar 2;129(9):1143-1154.1 This study involved patients (mostly younger than 60 years) with previously untreated FLT3 mutation-positive AML included in the UK AML15 and AML17 trials. Patients were randomised to receive either oral lestaurtinib (CEP701) or not after each of 4 cycles of induction and consolidation chemotherapy. As highlighted by the committee in the ACD, median OS in this study was slightly greater than 24 months in the control group, similar to the median OS observed in RATIFY. However, these data were obtained in a trial setting, and therefore are likely to include patients with a better prognosis compared with routine practice. Thus, the OS in these trials is likely to be longer than that observed in England in routine clinical practice.	Comment noted. The committee agreed that the mean overall survival better represented the whole population than the median overall survival. It also agreed that none of the mean overall survival values presented suggested that overall survival was below 24 months. Therefore midostaurin did not meet the short life expectancy criterion of less than 24 months. See FAD section 3.19.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Considering the evidence, the committee noted the Maynadie study (2013)2 which reported a median OS of less than 24 months but considered that this study "was not likely to be representative of the UK population because it was based on relatively old registry data from 1995 to 2002, and included people from countries where life expectancy is lower than in the UK". Given the inconsistent nature of the evidence available and to help the committee understand the survival of people newly diagnosed with FLT3 mutation-positive AML in the UK in a real-world setting, recent data on survival were obtained from a large UK registry, the Haematological Malignancy Research Network (HMRN). The HMRN database covers two adjacent former UK cancer networks (the Yorkshire Cancer Network and the Humber & Yorkshire Coast Cancer Network) with a total population of 3.8 million and collects detailed information about all haematological malignancies diagnosed in the region. Evidence from the HMRN database has been accepted by NICE to support decisions in previous appraisals. Data were obtained on cases of AML that were newly diagnosed between 2004 and 2015. A total of 1,572 patients were included in the HMRN database and 55.2% were male. Median (95% confidence intervals, CI) OS for the overall AML population included in the registry was [redacted]. When considering only people with FLT3 mutation-positive AML who received daunorubicin plus cytarabine as induction chemotherapy (i.e. corresponding to the licensed indication for midostaurin), median OS was [redacted]. In light of this additional real-world evidence regarding survival in people newly diagnosed with FLT3 mutation-positive AML, i.e. the population who would be eligible for midostaurin, we would ask the committee to reconsider its position regarding whether midostaurin meets the end-of life criteria. Registry data are likely to be more representative of routine clinical practice and thus the HRMN data are likely to be highly relevant, demonstrating that survival in people newly diagnosed with FLT3 mutation-positive AML in England is less than 24 months in current routine clinical practice.	
3	Company	Novartis Pharmaceuticals	3. Correction of inconsistencies identified following the changes introduced by the ERG Upon review of the model following the ERG changes, two inconsistencies were identified in the economic model in that: • the proportion of patients in the relapsed health state could become negative when the standardized mortality ratio (SMR) is greater than 2. As the ERG used a SMR of 4, the proportion of patients in the relapsed health state became negative at the end of the trace (this is implausible),	Comments noted. The committee accepted these corrections. See FAD section 3.18.

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			• amendments made by the ERG for the estimation of QALYs lead to double counting For transparency, an option has been added in the economic model in the "model parameters" sheet on cell 194 to allow the user to use the original or corrected version of the model. Further details can be found in the appendix, section 4.1.1.	
4	Company	Novartis Pharmaceuticals	4. Updated utility value in the relapsed health state to reflect published data and the definition of the health state used in the model In our original submission to NICE, the utility value for the relapsed health state was assumed to be 0.53 based on Pan et al, 2010.3 In their preferred model structure, the ERG assumed the utility value for the relapsed health state to be the same as the utility value for complete response (CR) in first line (CR1) (0.83). We understand some of the concerns expressed by the ERG due to the model structure not being able to capture the proportion of patients that may reach CR2 following successful subsequent therapy, and therefore we recognise that assuming a utility value of 0.53 for the relapse health state may underestimate HRQoL. However, conversely, we believe that assuming the utility value for the relapse health state to be the same as that for CR1 (as suggested by the ERG) is implausible and likely to be an overestimate. As mentioned by the ERG, patients with AML progress through a number of lines of therapy, and whilst patients move from CR to relapse between lines of treatments, the utility value for subsequent remissions is likely to be lower than the utility value for CR1. Furthermore, whilst some patients receiving second line therapy may experience remission, a proportion of patients may move directly to another relapse or supportive care and have a lower HRQoL. Leunis et al (2014)4 reported that the utility value in survivors after 1st relapse (0.78) was lower than for survivors who did not experience a relapse (0.83). We therefore believe that the utility value for the relapsed health state should be lower than that for CR1. We further believe that the utility value of 0.78 reported by Leunis et al (2014) does not include advanced stages of the disease, and therefore, we believe that the utility value for the relapsed health state in the model should be somewhere between the value of 0.53 used in the original model and 0.78. Further details are included in the appendix, section 4.1.2.	Comment noted. The committee concluded that 0.78 was the most plausible utility value for people in the relapsed health state. See FAD section 3.7.
5	Company	Novartis Pharmaceuticals	5. Cost in the relapse health state	Comments noted. The committee concluded that it was plausible that management costs would be closer to

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			In our original submission to NICE, the management cost per cycle for the relapsed health state was assumed to be £4,884, as derived from NICE TA3995 plus an additional one-off cost associated with the administration of a second line therapy (£9,161) at the point of relapse. In their preferred model structure, the ERG assumed the management cost for the relapsed health state to be zero. We understand the concern expressed by the ERG due to the model structure not being able to capture the proportion of patients that may reach CR2 following successful subsequent therapy. We therefore recognise that assuming a cost of £4,884 per cycle for the relapsed health state may be an overestimate. However, conversely, we believe that assuming a zero-management cost for the relapse health state is implausible and is likely to be a significant underestimate as management costs following relapse in first-line can be quite high. Whilst the cost for secondary therapy has been included as a one-off cost (£9,161) at the point of relapse, this cost only covers the administration of one subsequent line of chemotherapy and does not cover the costs of further lines of chemotherapy or management costs after first line. The assumption of non-zero costs for the relapsed health state and potentially high costs after first-line therapy is also supported by Wang et al (2014).6 Estimating the cost for the relapsed health state in our model is challenging, as this health state includes any subsequent health states following first-line treatment (CR2, relapse, supportive care etc) in people alive who are not in CR1 or who did not receive a transplant. Whilst uncertain, we believe a cost per cycle of £2,000 to be more appropriate based on the range of costs reported in Wang et al (2014) than the assumption of zero costs used by the ERG (with the exception of the one-off cost for secondary therapies that is included separately at the point of relapse). Further details can be found within the appendix, section 4.1.3.	£2,000 than £4,884 per cycle for the 3 years before people moved into the cured health state, in the committee's preferred model. See FAD section 3.9.
6	Company	Novartis Pharmaceuticals	6. Updated SMR to reflect the response obtained from 7 UK clinical experts and comments from the clinical experts at the NICE ACM In our original submission to NICE, we assumed that patients mortality in patients still alive at the end of the trial followed that of the general population, based on clinical advice. The ERG considered that patients with AML would die at a faster rate compared with the general population and assumed a SMR of 4. Whilst we understand that the mortality rate in people with AML may be slightly higher than that of the general population due to the presence of comorbidities, this is uncertain.	Comment noted. The committee concluded that although a 2-fold increase in mortality rate after the cure point was plausible, there was uncertainty and the true increase in mortality could be higher. See FAD section 3.10.

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			Clinical advice suggests that an SMR of 4 is likely to be an overestimate. This is supported by the view of the clinical experts during the NICE committee meeting which suggested a SMR of around 2. As mentioned in the ACD, "The clinical experts stated that they would expect mortality risk to increase following stem cell transplant, but that an overall 4-fold increase in mortality rate seemed high". In order to further inform this parameter, we asked 7 UK clinical experts to suggest what SMR they would expect to see in clinical practice in individuals with FLT3 mutation-positive AML compared to the general population. Clinical experts believed the SMR to range between [redacted]. Therefore, we believe that a SMR of 2 or less should be used and is more appropriate compared with the ERG assumption. Further details can be found within the appendix, section 4.1.4.	
7	Company	Novartis Pharmaceuticals	7. Alternative approach to age-adjustment The ERG considered that utility values should be adjusted by age to reflect the natural variation in utility by age. Different approaches can be used to age-adjust utility values. The ERG adjusted the utility value for age using the starting age in the model as an anchor. However, the utility values were sourced from studies that included a generally older population. Whilst we acknowledge that different approaches exist to adjust utility values by age, we consider that using the mean age of the patients in the different utility studies as an anchor when adjusting utility value by age to be more appropriate and reflective of the true utility values compared with using the starting age in the model. Further details can be found within the appendix, section 4.1.5.	Comment noted. The committee agreed that the company's method of adjusting utility values for age was appropriate. See FAD section 3.13.
8	Company	Novartis Pharmaceuticals	8. Bibliography 1. Knapper S, Russell N, Gilkes A et al. A randomized assessment of adding the kinase inhibitor lestaurtinib to first-line chemotherapy for FLT3-mutated AML. Blood 2017;129:1143-54. 2. Maynadie M, De Angelis R, Marcos-Gragera R et al. Survival of European patients diagnosed with myeloid malignancies: A HAEMACARE study. Haematologica 2013;98:230-8. 3. Pan F, Peng S, Fleurence R et al. Economic analysis of decitabine versus best supportive care in the treatment of intermediate- and high-risk myelodysplastic syndromes from a US payer perspective. Clin Ther 2010;32:2444-56.	N/A

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			4. Leunis A, Redekop WK, Uyl-de Groot CA, Lowenberg B. Impaired health-related quality of life in acute myeloid leukemia survivors: A single-center study. Eur J Haematol 2014;93:198-206. 5. National Institute for Health and Care Excellence. Technology assessment 399. July 2016. Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts. Available at: https://www.nice.org.uk/Guidance/TA399 Accessed February 2017. Wang HI, Aas E, Howell D et al. Long-term medical costs and life expectancy of acute myeloid leukemia: A probabilistic decision model. Value Health 2014;17:205-14.	
11	Consultee	NCRI-ACP-RCP	The NCRI-ACP-RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.	Comment noted. No action required.
12	Consultee	NCRI-ACP-RCP	We are happy that, in making its appraisal, the NICE Evidence Review Group has considered the relevant evidence concerning the use of midostaurin in AML. We also accept the adjustments that the ERG made to Novartis's base-case model as summarised in section 3.16 of the appraisal consultation document, with the possible exception of the decision to increase the maximum number of cycles of maintenance therapy from 12 to 18 (given that only a very limited number of patients in the RATIFY study went on to receive 18 cycles and that approval is currently being sought for 12 cycles of maintenance therapy).	Comment noted. The committee considered that the cost data in the model should be consistent with the clinical data. It considered that the data in the model should be taken from the trial. However, because of the small number of people who had more than 12 cycles, increasing the maximum cycle length to 18 had a limited effect on the ICER. See FAD section 3.11.
13	Consultee	NCRI-ACP-RCP	We agree with the conclusion reached in the appraisal consultation document that the RATIFY study clearly showed that midostaurin with chemotherapy was significantly more clinically-effective than chemotherapy alone in terms of both improved overall survival and event-free survival for patients with FLT3-mutated newly-diagnosed AML This represents an innovative, potential advance in AML intensive treatment schedules that have not been significantly improved for >30 years. The separation in survival curves demonstrated by the RATIFY study (published in NEJM 2017) occurs, however, in the early stages of chemotherapy treatment, suggesting that the principal clinical benefit from midostaurin is likely to be derived from its initial combination with chemotherapy (induction and consolidation) rather than in its subsequent use as post-chemotherapy maintenance treatment. Only a relatively small proportion of RATIFY study patients received midostaurin maintenance. Indeed, US approvals for midostaurin have been for its use in combination with chemotherapy but NOT in subsequent maintenance therapy. Proportionately a large part of the costs of midostaurin lie in administering it as maintenance therapy. Given the failure of the NICE ERG to demonstrate a clear cost-benefit from midostaurin when used with chemotherapy AND as maintenance, we would suggest that the committee now also considers whether this intervention would meet cost-effectiveness criteria if restricted to use with chemotherapy (but not used as maintenance).	Comment noted. The marketing authorisation for midostaurin includes maintenance therapy. In accordance with the Guide to the methods of technology appraisal 2013 section 6.1.12, for this topic the appraisal committee made recommendations regarding the use of midostaurin within the terms of its UK marketing authorisation. See FAD section 3.2.

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14	Consultee	Leukaemia CARE	We are concerned by the committee's conclusion that midostaurin does not meet the criteria to be considered a life-extending treatment at the end of life. Whilst we are pleased to see that the committee acknowledged the survival benefit of midostaurin as meeting the life extending criterion (3.19), with regards to the short life expectancy criterion: As highlighted in our original submission, we would question the applicability of the overall survival figure for the placebo arm of the RATIFY trial (25.59 months), as the RATIFY trial did not have any UK sites. As such, the OS data for the placebo arm is not directly representative of the expected survival of UK patients, as UK survival for AML is significantly lower (approximately 90%) than the European Average. Applying EUROCARE 5 data (1) to the RATIFY comparator arm survival figure, we expect overall survival in this setting (for patients who do not receive midostaurin) to be approximately 23.2 months. Furthermore, as stated in the ACD "the mean age of people likely to be eligible for midostaurin in England is higher than the mean age of people in the trial" (3.3). AML mortality is strongly related to age, with the highest mortality rates being in older patients, as highlighted in Leukaemia Care's 'I wasn't born yesterday' report (2). An analysis of Cancer Research UK 2014 mortality data (3) shows that an AML patient aged 60 and older is twice as likely to die from their AML than a patient aged less than 60. With increasing numbers of older patients being treated with intensive chemotherapy, this will reduce the survival estimate in this setting (in the absence of midostaurin). As such, the most likely survival estimate in this setting (in the absence of midostaurin) is less than 24 months. Therefore, midostaurin satisfies both criteria to be considered a life-extending treatment at the end of life. 1) EUROCARE 5 - http://www.eurocare.it/ 2) Leukaemia Care, I wasn't Born Yesterday, pg.7 http://www.leukaemiacare.org.uk/resources/leukaemia-i-wasnt-born-yesterday 3) CRUK Mortality Data http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/mortality	Comments noted. The committee considered evidence from the Haematological Malignancy Research Network. The committee agreed that the mean overall survival better represented the whole population than the median overall survival. It also agreed that none of the mean overall survival values presented suggested that overall survival was below 24 months. Therefore midostaurin did not meet the short life expectancy criterion of less than 24 months. See FAD section 3.19.

The following consultees/commentators indicated that they had no comments on the appraisal consultation document:

Department of Health and Social Care

Midostaurin for untreated acute myeloid leukaemia [ID894]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 4 January 2018 **email:** tacommc@nice.org.uk or NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Novartis Pharmaceuticals Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1. Factual inaccuracies	In the slides presented to the committee, the ERG explained the impact on the ICER resulting from each change to the model, both individually and cumulatively. We believe that these analyses were mislabelled by the ERG, in that the change in the ICER reported did not correspond to the correct change in the model. Whilst this does not affect the ERG base-case, we believe that the mislabelling could have misled the committee on drivers of the ICER. We believe the correct labelling of the table shown in slide 19 of the ACM papers to be that shown in the appendix, table 1.
2. Additional evidence supportive to End of Life	Considering the evidence, the committee felt that the survival in people newly diagnosed with FLT3 mutation-positive AML was more than 24 months, based on a study conducted by Knapper et al (2017) and the median OS of 26 months from the RATIFY trial. Whilst the exact reference of the Knapper study (2017) considered by the committee is not included in the ACD, we believe that the committee referred to the following study: Knapper et al. Blood. 2017 Mar 2;129(9):1143-1154.[1]

	This study involved patients (mostly younger than 60 years) with previously untreated FLT3 mutation-positive AML included in the UK AML15 and AML17 trials. Patients were randomised to receive either oral lestaurtinib (CEP701) or not after each of 4 cycles of induction and consolidation chemotherapy. As highlighted by the committee in the ACD, median OS in this study was slightly greater than 24 months in the control group, similar to the median OS observed in RATIFY. However, these data were obtained in a trial setting, and therefore are likely to include patients with a better prognosis compared with routine practice. Thus, the OS in these trials is likely to be longer than that observed in England in routine clinical practice. Considering the evidence, the committee noted the Maynadie study (2013)[2] which reported a median OS of less than 24 months but considered that this study "was not likely to be representative of the UK population because it was based on relatively old registry data from 1995 to 2002, and included people from countries where life expectancy is lower than in the UK". Given the inconsistent nature of the evidence available and to help the committee understand the survival of people newly diagnosed with FLT3 mutation-positive AML in the UK in a real-world setting, recent data on survival were obtained from a large UK registry, the Haematological Malignancy Research Network (HMRN). The HMRN database covers two adjacent former UK cancer networks (the Yorkshire Cancer Network and the Humber & Yorkshire Coast Cancer Network) with a total population of 3.8 million and collects detailed information about all haematological malignancies diagnosed in the region. Evidence from the HMRN database has been accepted by NICE to support decisions in previous appraisals. Data were obtained on cases of AML that were newly diagnosed between 2004 and 2015. A total of 1,572 patients were included in the HMRN database and 55.2% were male. Median (95% confidence intervals, CI) OS for the overall AML population included in the registry was [redacted]. When considering only people with FLT3 mutation-positive AML who received daunorubicin plus cytarabine as induction chemotherapy

	(i.e. corresponding to the licensed indication for midostaurin), median OS was [redacted]. In light of this additional real-world evidence regarding survival in people newly diagnosed with FLT3 mutation-positive AML, i.e. the population who would be eligible for midostaurin, we would ask the committee to reconsider its position regarding whether midostaurin meets the end-of life criteria. Registry data are likely to be more representative of routine clinical practice and thus the HRMN data are likely to be highly relevant, demonstrating that survival in people newly diagnosed with FLT3 mutation-positive AML in England is less than 24 months in current routine clinical practice.
3. Correction of inconsistencies identified following the changes introduced by the ERG	Upon review of the model following the ERG changes, two inconsistencies were identified in the economic model in that: - the proportion of patients in the relapsed health state could become negative when the standardized mortality ratio (SMR) is greater than 2. As the ERG used a SMR of 4, the proportion of patients in the relapsed health state became negative at the end of the trace (this is implausible), - amendments made by the ERG for the estimation of QALYs lead to double counting For transparency, an option has been added in the economic model in the "model parameters" sheet on cell 194 to allow the user to use the original or corrected version of the model. Further details can be found in the appendix, section 4.1.1.
4. Updated utility value in the relapsed health state to reflect published data and the definition of the health state used in the model	In our original submission to NICE, the utility value for the relapsed health state was assumed to be 0.53 based on Pan et al, 2010.[3] In their preferred model structure, the ERG assumed the utility value for the relapsed health state to be the same as the utility value for complete response (CR) in first line (CR1) (0.83). We understand some of the concerns expressed by the ERG due to the model structure not being able to capture the proportion of patients that may reach CR2 following successful subsequent therapy, and therefore we recognise that assuming a utility value of 0.53 for the relapse health state may underestimate HRQoL. However, conversely, we believe that assuming the utility value for the relapse health state to be the same as that for CR1 (as suggested by the ERG) is implausible and

	likely to be an overestimate. As mentioned by the ERG, patients with AML progress through a number of lines of therapy, and whilst patients move from CR to relapse between lines of treatments, the utility value for subsequent remissions is likely to be lower than the utility value for CR1. Furthermore, whilst some patients receiving second line therapy may experience remission, a proportion of patients may move directly to another relapse or supportive care and have a lower HRQoL. Leunis et al (2014)[4] reported that the utility value in survivors after 1st relapse (0.78) was lower than for survivors who did not experience a relapse (0.83). We therefore believe that the utility value for the relapsed health state should be lower than that for CR1. We further believe that the utility value of 0.78 reported by Leunis et al (2014) does not include advanced stages of the disease, and therefore, we believe that the utility value for the relapsed health state in the model should be somewhere between the value of 0.53 used in the original model and 0.78. Further details are included in the appendix, section 4.1.2.
5. Cost in the relapse health state	In our original submission to NICE, the management cost per cycle for the relapsed health state was assumed to be £4,884, as derived from NICE TA399[5] plus an additional one-off cost associated with the administration of a second line therapy (£9,161) at the point of relapse. In their preferred model structure, the ERG assumed the management cost for the relapsed health state to be zero. We understand the concern expressed by the ERG due to the model structure not being able to capture the proportion of patients that may reach CR2 following successful subsequent therapy. We therefore recognise that assuming a cost of £4,884 per cycle for the relapsed health state may be an overestimate. However, conversely, we believe that assuming a zero-management cost for the relapse health state is implausible and is likely to be a significant underestimate as management costs following relapse in first-line can be quite high. Whilst the cost for secondary therapy has been included as a one-off cost (£9,161) at the point of relapse, this cost only covers the administration of one subsequent line of chemotherapy and does not cover the costs of further lines of chemotherapy or management costs after first line.

	The assumption of non-zero costs for the relapsed health state and potentially high costs after first-line therapy is also supported by Wang et al (2014).[6] Estimating the cost for the relapsed health state in our model is challenging, as this health state includes any subsequent health states following first-line treatment (CR2, relapse, supportive care etc) in people alive who are not in CR1 or who did not receive a transplant. Whilst uncertain, we believe a cost per cycle of £2,000 to be more appropriate based on the range of costs reported in Wang et al (2014) than the assumption of zero costs used by the ERG (with the exception of the one-off cost for secondary therapies that is included separately at the point of relapse). Further details can be found within the appendix, section 4.1.3.
6. Updated SMR to reflect the response obtained from 7 UK clinical experts and comments from the clinical experts at the NICE ACM	In our original submission to NICE, we assumed that patients mortality in patients still alive at the end of the trial followed that of the general population, based on clinical advice. The ERG considered that patients with AML would die at a faster rate compared with the general population and assumed a SMR of 4. Whilst we understand that the mortality rate in people with AML may be slightly higher than that of the general population due to the presence of comorbidities, this is uncertain. Clinical advice suggests that an SMR of 4 is likely to be an overestimate. This is supported by the view of the clinical experts during the NICE committee meeting which suggested a SMR of around 2. As mentioned in the ACD, “The clinical experts stated that they would expect mortality risk to increase following stem cell transplant, but that an overall 4-fold increase in mortality rate seemed high”. In order to further inform this parameter, we asked 7 UK clinical experts to suggest what SMR they would expect to see in clinical practice in individuals with FLT3 mutation-positive AML compared to the general population. Clinical experts believed the SMR to range between [redacted].

	Therefore, we believe that a SMR of 2 or less should be used and is more appropriate compared with the ERG assumption. Further details can be found within the appendix, section 4.1.4.
7. Alternative approach to age-adjustment	The ERG considered that utility values should be adjusted by age to reflect the natural variation in utility by age. Different approaches can be used to age-adjust utility values. The ERG adjusted the utility value for age using the starting age in the model as an anchor. However, the utility values were sourced from studies that included a generally older population. Whilst we acknowledge that different approaches exist to adjust utility values by age, we consider that using the mean age of the patients in the different utility studies as an anchor when adjusting utility value by age to be more appropriate and reflective of the true utility values compared with using the starting age in the model. Further details can be found within the appendix, section 4.1.5.
8. Bibliography	1. Knapper S, Russell N, Gilkes A *et al.* A randomized assessment of adding the kinase inhibitor lestaurtinib to first-line chemotherapy for FLT3-mutated AML. *Blood* 2017;129:1143-54. 2. Maynadie M, De Angelis R, Marcos-Gragera R *et al.* Survival of European patients diagnosed with myeloid malignancies: A HAEMACARE study. *Haematologica* 2013;98:230-8. 3. Pan F, Peng S, Fleurence R *et al.* Economic analysis of decitabine versus best supportive care in the treatment of intermediate- and high-risk myelodysplastic syndromes from a US payer perspective. *Clin Ther* 2010;32:2444-56. 4. Leunis A, Redekop WK, Uyl-de Groot CA, Lowenberg B. Impaired health-related quality of life in acute myeloid leukemia survivors: A single-center study. *Eur J Haematol* 2014;93:198-206. 5. National Institute for Health and Care Excellence. Technology assessment 399. July 2016. Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts. Available at: https://www.nice.org.uk/Guidance/TA399 Accessed February 2017. 6. Wang HI, Aas E, Howell D *et al.* Long-term medical costs and life expectancy of acute myeloid leukemia: A probabilistic decision model. *Value Health* 2014;17:205-14.

Insert extra rows as needed

Analysis of overall survival in patients newly diagnosed with AML in the UK, based on data obtained from the Haematological Malignancy Research Network

Methods

The analysis is based on cases of acute myeloid leukaemia (AML) that were newly diagnosed 2004-2015 in the Haematological Malignancy Research Network (HMRN), an ongoing population-based cohort, which was established in 2004 to provide robust, generalizable data to inform clinical practice and research on haematological malignancies. The HMRN region comprises a total population of 3.8 million (covering the area formerly served by the Yorkshire and the Humber & Yorkshire Coast Cancer Networks). All haematological malignancy diagnoses within the region are made at a single specialist haematopathology laboratory – the Haematological Malignancy Diagnostic Service (HMDS) and it is from here that all HMRN patients are ascertained. All diagnoses, including disease transformations and progressions, are automatically coded to International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). Data collection is initiated six months after date of diagnosis.

Standard statistical methods have been used to describe the demographics, prognostics and disease management of these patients including mapping each patient's treatment pathway from date of diagnosis to end of follow up. Time to event analyses including Kaplan-Meier have been used to estimate the overall survival (OS) and event-free survival (EFS) by demographic and baseline prognostic and clinical characteristics. Patients still alive at the time of the analyses were censored on the 25th May 2017.

Results

Table 1 Patient baseline characteristics

		Total n (%)
Total		[redacted]
Sex	Male	[redacted]
	Female	[redacted]
Age at diagnosis (years)	Mean (SD)	[redacted]
	Median (Range)	[redacted]
Age group	<60	[redacted]
	≥60	[redacted]
ICD-O-3	AML NOS	[redacted]
	AML with myelodysplasia-related changes	[redacted]
	AML probable therapy related	[redacted]
	AML with NPM mutation as sole abnormality	[redacted]
	AML with core binding factors	[redacted]
	AML with MLL (11q23) rearrangement	[redacted]
De novo diagnosis[1]	No	[redacted]
	Yes	[redacted]
Data collection	Yes	
	No	[redacted]

[1]Myelodysplastic syndromes (n=203), Myelodysplastic/ Myeloproliferative neoplasms (n=42), Myeloproliferative neoplasms (n=30), Myelofibrosis (n=10), Chronic lymphocytic leukaemia (n=6), Diffuse large B-cell lymphoma (n=5), AML (n=4), Mantle cell lymphoma (n=3), Monoclonal gammopathy of undetermined significance (MGUS) (n=3), B-lymphoblastic leukaemia (n=2), Acute promyelocytic leukaemia (n=1), Burkitt lymphoma (n=1), Classic Hodgkin lymphoma (n=1), Systemic marginal zone lymphoma (n=1), T-cell leukaemia (n=1)

Table 2 First line treatment by age group, sex and FLT3-mutation status

	Total n (%)	Age group n (%)		Sex n (%)		FLT 3 n (%)		
		<60	≥60	Male	Female	Internal Tandem Duplication Mutation (ITD)	Wild Type	Not Tested
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intensive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-intensive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supportive/palliative care only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other[2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observation only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Data collection not done	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] Trial participation AML14 (n=13), AML15 (n=111), AML16 (n=154), AML17 (n=131), AML 18 (n=14), LI-1 (n=24), RAVVA (n=7), DEC-MDS (n=1)
[2] Treated for a more serious non-haematological comorbidity, refused treatment or died prior to treatment

Median (95% confidence intervals, CI) and mean (SD) overall survival in patients with FLT3 mutation-positive AML who received daunorubicin plus cytarabine as induction therapy was [redacted] years and [redacted] years, respectively (Figure 1).

Figure 1 Overall survival in patients with FLT3 mutation-positive AML who received daunorubicin plus cytarabine as induction therapy

Demographic and disease characteristics in patients newly diagnosed with AML in the UK, based on data obtained from the Haematological Malignancy Research Network

Methods

The analysis is based on cases of acute myeloid leukaemia (AML) that were newly diagnosed 2004-2015 in the Haematological Malignancy Research Network (HMRN), an ongoing population-based cohort, which was established in 2004 to provide robust, generalizable data to inform clinical practice and research on haematological malignancies. The HMRN region comprises a total population of 3.8 million (covering the area formerly served by the Yorkshire and the Humber & Yorkshire Coast Cancer Networks). All haematological malignancy diagnoses within the region are made at a single specialist haematopathology laboratory – the Haematological Malignancy Diagnostic Service (HMDS) and it is from here that all HMRN patients are ascertained. All diagnoses, including disease transformations and progressions, are automatically coded to International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). Data collection is initiated six months after date of diagnosis.

Standard statistical methods have been used to describe the demographics, prognostics and disease management of these patients including mapping each patient's treatment pathway from date of diagnosis to end of follow up. Time to event analyses including Kaplan-Meier have been used to estimate the overall survival (OS) and event-free survival (EFS) by demographic and baseline prognostic and clinical characteristics. Patients still alive at the time of the analyses were censored on the 25th May 2017.

Results

Baseline characteristics of the overall population are summarised in Table 1. The mean (SD) age of the overall population at diagnosis was [redacted] years. In the subgroup corresponding to the midostaurin licence (ie who received intensive chemotherapy and had FLT3 mutation-positive AML), the mean age was [redacted]

Results

Table 1 Patient baseline characteristics

		Total n (%)
Total		[redacted]
Sex	Male	[redacted]
	Female	[redacted]
Age at diagnosis (years)	Mean (SD)	[redacted]
	Median (Range)	[redacted]
Age group	<60	[redacted]
	≥60	[redacted]
ICD-O-3	AML NOS	[redacted]
	AML with myelodysplasia-related changes	[redacted]
	AML probable therapy related	[redacted]
	AML with NPM mutation as sole abnormality	[redacted]
	AML with core binding factors	[redacted]
	AML with MLL (11q23) rearrangement	[redacted]
De novo diagnosis[1]	No	[redacted]
	Yes	[redacted]
Data collection	Yes	
	No	[redacted]

[1]Myelodysplastic syndromes (n=203), Myelodysplastic/ Myeloproliferative neoplasms (n=42), Myeloproliferative neoplasms (n=30), Myelofibrosis (n=10), Chronic lymphocytic leukaemia (n=6), Diffuse large B-cell lymphoma (n=5), AML (n=4), Mantle cell lymphoma (n=3), Monoclonal gammopathy of undetermined significance (MGUS) (n=3), B-lymphoblastic leukaemia (n=2), Acute promyelocytic leukaemia (n=1), Burkitt lymphoma (n=1), Classic Hodgkin lymphoma (n=1), Systemic marginal zone lymphoma (n=1), T-cell leukaemia (n=1)

Midostaurin for untreated acute myeloid leukaemia [ID894]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 4 January 2018 **email:** tacommc@nice.org.uk or NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCP
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted], [redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
General	The NCRI-ACP-RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.
1	We are happy that, in making its appraisal, the NICE Evidence Review Group has considered the relevant evidence concerning the use of midostaurin in AML. We also accept the adjustments that the ERG made to Novartis's base-case model as summarised in section 3.16 of the appraisal consultation document, with the possible exception of the decision to increase the maximum number of cycles of maintenance therapy from 12 to 18 (given that only a very limited number of patients in the RATIFY study went on to receive 18 cycles and that approval is currently being sought for 12 cycles of maintenance therapy).
2	We agree with the conclusion reached in the appraisal consultation document that the RATIFY study clearly showed that midostaurin with chemotherapy was significantly more clinically-effective than chemotherapy alone in terms of both improved overall survival and event-free survival for patients with FLT3-mutated newly-diagnosed AML This represents an innovative, potential advance in AML intensive treatment schedules that have not been significantly improved for >30 years. The separation in survival curves demonstrated by the RATIFY study (published in NEJM 2017) occurs, however, in the early stages of chemotherapy treatment, suggesting that the principal clinical benefit from midostaurin is likely to be derived from its initial combination with chemotherapy (induction and consolidation) rather than in its subsequent use as post-chemotherapy maintenance treatment. Only a relatively small proportion of RATIFY study patients received midostaurin

	maintenance. Indeed, US approvals for midostaurin have been for its use in combination with chemotherapy but NOT in subsequent maintenance therapy. Proportionately a large part of the costs of midostaurin lie in administering it as maintenance therapy. Given the failure of the NICE ERG to demonstrate a clear cost-benefit from midostaurin when used with chemotherapy AND as maintenance, we would suggest that the committee now also considers whether this intervention would meet cost-effectiveness criteria if restricted to use with chemotherapy (but not used as maintenance).

Insert extra rows as needed

Midostaurin for untreated acute myeloid leukaemia [ID894]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 4 January 2018 **email:** tacommc@nice.org.uk or NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Leukaemia Care
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted], Leukaemia Care

Midostaurin for untreated acute myeloid leukaemia [ID894]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 4 January 2018 **email:** tacommc@nice.org.uk or NICE DOCS

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned by the committee's conclusion that midostaurin does not meet the criteria to be considered a life-extending treatment at the end of life. Whilst we are pleased to see that the committee acknowledged the survival benefit of midostaurin as meeting the life extending criterion (3.19), with regards to the short life expectancy criterion: As highlighted in our original submission, we would question the applicability of the overall survival figure for the placebo arm of the RATIFY trial (25.59 months), as the RATIFY trial did not have any UK sites. As such, the OS data for the placebo arm is not directly representative of the expected survival of UK patients, as UK survival for AML is significantly lower (approximately 90%) than the European Average. Applying EUROCARE 5 data (1) to the RATIFY comparator arm survival figure, we expect overall survival in this setting (for patients who do not receive midostaurin) to be approximately 23.2 months. Furthermore, as stated in the ACD "the mean age of people likely to be eligible for midostaurin in England is higher than the mean age of people in the trial" (3.3). AML mortality is strongly related to age, with the highest mortality rates being in older patients, as highlighted in Leukaemia Care's 'I wasn't born yesterday' report (2). An analysis of Cancer Research UK 2014 mortality data (3) shows that an AML patient aged 60 and older is twice as likely to die from their AML than a patient aged less than 60. With increasing numbers of older patients being treated with intensive chemotherapy, this will reduce the survival estimate in this setting (in the absence of midostaurin). As such, the most likely survival estimate in this setting (in the absence of midostaurin) is less than 24 months. Therefore, midostaurin satisfies both criteria to be considered a life-extending treatment at the end of life. 1) EUROCARE 5 - http://www.eurocare.it/ 2) Leukaemia Care, I wasn't Born Yesterday, pg.7 http://www.leukaemiacare.org.uk/resources/leukaemia-i-wasnt-born-yesterday 3) CRUK Mortality Data http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/mortality

Insert extra rows as needed

National Institute for Health and Clinical Excellence

Midostaurin for untreated acute myeloid leukaemia

RESPONSE TO APPRAISAL CONSULTATION DOCUMENT

04 January 2018

1 Summary

Novartis has provided a submission in which the base case ICER for midostaurin was £28,465 per QALY gained. This was based on an analysis using data from the RATIFY trial. Following the review performed by the evidence review group (ERG), the Appraisal Committee (AC) concluded that the most plausible ICER was £62,810 based on the ERG's preferred assumptions. As a result, the Committee's preliminary recommendation is that midostaurin is not recommended.

Novartis would like the Committee to reconsider its recommendation in the light of: 1) additional evidence for the survival of patients with FLT3 mutation-positive AML which indicates midostaurin meets the end of life criteria, 2) revisions to the ERG base-case and 3) implementation of a new confidential PAS.

Firstly, additional data/evidence are now available regarding survival in patients with FLT3 mutation-positive AML from an analysis of data collected by the Haematological Malignancy Research Network (HMRN). These data indicate that for patients with FLT3 mutation-positive AML who are eligible for intensive chemotherapy i.e. those eligible for midostaurin treatment, median overall survival (OS) is [redacted]. Hence most patients survive for less than the 24 months and thus midostaurin meets the NICE "end of life" criteria.

Secondly, Novartis considers that a number of changes to the model made by the ERG are inappropriate or are not supported by evidence. Novartis have therefore revised the ERG's preferred base-case ICER (£62,810) to take into account: (a) additional evidence on the rate of death in patients with FLT3 mutation-positive AML provided by 7 UK clinical experts, (b) incorporation of a utility value and costs for the relapsed heath state that is more in line with the definition used in the model and is supported by published evidence and (c) a more appropriate approach to adjust utility by age, given the mean age of patients in the study used to provide clinical data for the model. In addition, two inconsistencies in the ERG model were identified and have been corrected. Correction of the inconsistencies and incorporating the additional evidence reduces the ICER from £62,810 (ERG base-case before correction) to £31,626 without PAS.

Thirdly, a confidential PAS has also been offered by the manufacturer. Midostaurin would be offered to the NHS at a discount price corresponding to a [redacted]. Taking into account the confidential PAS, the ICER is reduced from [redacted] (ERG base-case after PAS) to [redacted]

2 Factual inaccuracies

In the slides presented to the committee, the ERG explained the impact on the ICER resulting from each change to the model, both individually and cumulatively. We believe that these analyses were mislabelled by the ERG, in that the change in the ICER reported did not correspond to the correct change in the model. Whilst this does not affect the ERG base-case, we believe that the mislabelling could have misled the committee on drivers of the ICER.

We believe the correct labelling of the table shown in slide 19 to be that given in Table 1.

Table 1 Impact of changes on the ICER

	Individual impact on the ICER	**Cumulative impact**
ERG's preferred model structure (new cured state, zero health state costs in CR 1L and post-SCT recovery states)	£39,720	£39,720
Maximum number of cycles of monotherapy increased to 18 (based on RATIFY)	£28,569	£39,835
Age-adjusted utilities applied	£30,354	£42,734
Units of treatment received based on company's original model (discrepancy corrected)	£39,904	£45,937
Adverse events associated with SCT applied	£30,869	£49,778
Applying a 4-fold risk to general population mortality	£28,699	£62,810

3 Additional evidence supportive to End of Life

Considering the evidence, the committee felt that the survival in people newly diagnosed with FLT3 mutation-positive AML was more than 24 months, based on a study conducted by Knapper et al (2017) and the median OS of 26 months from the RATIFY trial.

Whilst the exact reference of the Knapper study (2017) considered by the committee is not included in the ACD, we believe that the committee referred to the following study: Knapper et al. Blood. 2017 Mar 2;129(9):1143-1154.[1]

This study involved patients (mostly younger than 60 years) with previously untreated FLT3 mutation-positive AML included in the UK AML15 and AML17 trials. Patients were randomised to receive either oral lestaurtinib (CEP701) or not after each of 4 cycles of induction and consolidation chemotherapy.

As highlighted by the committee in the ACD, median OS in this study was slightly greater than 24 months in the control group, similar to the median OS observed in RATIFY.

However, these data were obtained in a trial setting, and therefore are likely to include patients with a better prognosis compared with routine practice. Thus, the OS in these trials is likely to be longer than that observed in England in routine clinical practice.

Considering the evidence, the committee noted the Maynadie study (2013)[2] which reported a median OS of less than 24 months but considered that this study "*was not likely to be representative of the UK population because it was based on relatively old registry data from 1995 to 2002, and included people from countries where life expectancy is lower than in the UK*".

Given the inconsistent nature of the evidence available and to help the committee understand the survival of people newly diagnosed with FLT3 mutation-positive AML in the UK in a real-world setting, recent data on survival were obtained from a large UK registry, the Haematological Malignancy Research Network (HMRN). The HMRN database covers two adjacent former UK cancer networks (the Yorkshire Cancer Network and the Humber & Yorkshire Coast Cancer Network) with a total population of 3.8 million and collects detailed

information about all haematological malignancies diagnosed in the region. Evidence from the HMRN database has been accepted by NICE to support decisions in previous appraisals.

Data were obtained on cases of AML that were newly diagnosed between 2004-2015. A total of 1,572 patients were included in the HMRN database and 55.2% were male.

Median (95% confidence intervals, CI) OS for the overall AML population included in the registry was [redacted] When considering only people with FLT3 mutation-positive AML who received daunorubicin plus cytarabine as induction chemotherapy (i.e. corresponding to the licensed indication for midostaurin), median OS was [redacted]

In light of this additional real-world evidence regarding survival in people newly diagnosed with FLT3 mutation-positive AML, i.e. the population who would be eligible for midostaurin, we would ask the committee to reconsider its position regarding whether midostaurin meets the end-of life criteria. Registry data are likely to be more representative of routine clinical practice and thus the HRMN data are likely to be more relevant, demonstrating that survival in people newly diagnosed with FLT3 mutation-positive AML in England is less than 24 months in current routine clinical practice.

4 Revised base-case

A revised base-case is presented which incorporates the following changes in addition to correcting the inconsistencies identified following the changes introduced by the ERG: (a) a new standardized mortality ratio (SMR) informed by a UK clinical survey, (b) updated utility values for the relapse health state in line with published evidence and the definition of this health state, (c) updated management costs for the relapse health state supported by data from a previously published economic model and (d) an alternative approach to adjust the utility value according to age.

4.1 Description of the changes

The following changes were made to the ERG base case model.

4.1.1 Correction of inconsistencies identified following the changes introduced by the ERG

Upon review of the model following the ERG changes, two inconsistencies were identified in the economic model in that:

- the proportion of patients in the relapsed health state could become negative when the SMR is greater than 2. As the ERG used a SMR of 4, the proportion of patients in the relapsed health state became negative at the end of the trace (this is implausible),
- amendments made by the ERG for the estimation of QALYs lead to double counting

For transparency, an option has been added in the economic model in the "model parameters" sheet on cell 194 to allow the user to use the original or corrected version of the model.

Correcting these inconsistencies have a very minimal impact on the ICER, decreasing the ERG base-case ICER from £62,810 to £62,712 per QALY gained.

Inconsistency 1: Negative proportion of patients in the relapsed health state

This is because the model uses a partitioned survival approach whereby OS and complete response (CR) [which uses event-free survival (EFS)] are extrapolated independently from each other, despite being correlated (the same events are included in OS and EFS). When assuming an SMR greater than 2, the rate of death becomes larger. However, CR remained

extrapolated using the extrapolation from the EFS curve which follow the trend from the trial but not the OS extrapolation used in the model which uses an SMR.

Because of the disconnect between the OS and CR/EFS extrapolations in the model, negative values were generated for the relapse health state at the end of the trace when an SMR of 4 was used by the ERG.

Therefore, following identification of this inconsistency, we corrected it by assuming the same extrapolation (based on rate of death from general population plus SMR) between OS and CR/EFS to avoid generating negative values. This is in line with the comment from the ERG on page 77 where concerns were expressed that EFS includes death but OS and EFS are extrapolated independently from each other.

Changes to correct for this inconsistency (using the extrapolation for OS using the SMR for CR extrapolation beyond the trial period) were made in the "Appendix Extrapolation" sheet in Column DS to DV, from row 106.

Inconsistency 2: Double counting of QALYs in the relapse health state

In its preferred base-case, the ERG made a further adjustment, assuming that people receiving secondary therapy experience an additional utility value of 0.30 based on the difference between the utility for relapse (0.53) and utility for CR (0.83).

This adjustment is not appropriate as it overestimates the number of QALYs. When patients receive secondary therapy, they are effectively in relapse. Therefore adding a utility value of 0.30 to the proportion of patients in secondary therapy in addition to the utility value for relapse (0.83 as assumed by the ERG in its base-case) will lead to double counting. This is because secondary therapy is not a 'true' health state in the model, but is used for costing purpose.

Such an approach is inconsistent and favours standard therapy, as fewer people in the midostaurin arm relapsed and received secondary therapy.

Therefore, we believe that the adjustment made by the ERG (increasing the utility value for secondary therapy) is incorrect. In its base-case the ERG assumes a utility value of 0.83 for

relapse (as for CR). We therefore believe that the ERG aimed instead to reduce the utility value for relapse by 0.30 at the point of secondary therapy (one cycle).

Changes to correct for this inconsistency (removing the additional utility value applied to secondary therapy) were made in the "Appendix Transition" sheet in Column BV.

4.1.2 Updated utility value in the relapsed health state to reflect published data and the definition of the health state used in the model

In our original submission to NICE, the utility value for the relapsed health state was assumed to be 0.53 based on Pan et al, 2010.[3] In their preferred model structure, the ERG assumed the utility value for the relapsed health state to be the same as the utility value for CR in first line (0.83).

We understand some of the concerns expressed by the ERG due to the model structure not being able to capture the proportion of patients that may reach CR2 following successful subsequent therapy, and therefore we recognise that assuming a utility value of 0.53 for the relapse health state may underestimate HRQoL.

However, conversely, we believe that assuming the utility value for the relapse health state to be the same as CR in first line (as suggested by the ERG) is implausible and likely to be an overestimate. As mentioned by the ERG, patients with AML go through a number of lines of therapy, and whilst patients move from CR to relapse between lines of treatments, the utility value after first line therapy is likely to be lower than the utility value in CR1. Furthermore, whilst some patients receiving second line therapy may experience remission, a proportion of patients may move directly to another relapse or supportive care and have a lower HRQoL.

The lower utility value following relapse in first-line is supported by evidence. For instance, Leunis et al, 2014[4] reported a utility value of 0.83 in long-term survivors who did not experience a relapse and 0.78 in long-term survivors who experienced a relapse following first line therapy. Our relapse health state includes any subsequent lines of treatment. Therefore, the utility value for this health state should at least be lower than 0.78. The value reported by Leunis et al (2014) also does not include severity of the disease. Therefore, we believe that, whilst

uncertain, the utility value for the relapse health state (to reflect the definition of this health state in our model) should be in-between 0.78 and 0.53.

As suggested by the ERG, following relapse in first-line, patients may receive second-line therapy and experience CR2. Lee et al (2009)[5] showed that amongst 61 patients (median age, 33.6 yr) with relapsed or refractory AML treated with FLAG without idarubicin 29 patients (47.5%) achieved a CR. In addition, a single-centre study by Pastore et al (2003)[6] in people with relapsed/refractory AML treated with FLAG-IDA (n=46) reported a CR of 52.1%.

Therefore, whilst some patients may experience CR2, approximately half of patients would not experience remission in second-line and are likely to have a worse HRQoL. In addition, the remission may not be prolonged.

We believed that the utility value for the relapsed health state should at least be 0.78 based on Leunis et al (2014) and lower than the utility value use for CR in first-line. However, as highlighted we also believe that the utility value for the relapsed health state is somewhere in between 0.78 and 0.53. Consequently, given the uncertainty, we consider that using the mid-point between the value of 0.78 and 0.53 would represent a more plausible estimate compared with the ERG value (0.83) which assumes no difference in HRQoL between first-line and subsequent lines. Therefore a utility value of 0.655 was used in our revised base-case. We feel that this value is more in line with our health state definition and is supported by published evidence.

Assuming the utility value for the relapsed health state to be 0.655 instead of 0.83 (as assumed by the ERG) reduces the ICER from £62,712 to £55,579 without PAS.

4.1.3 Cost in the relapse health state

In our original submission to NICE, the management cost per cycle for the relapsed health state was assumed to be £4,884, as derived from NICE TA399[7] plus an additional one- off cost associated with the administration of a second line therapy (£9,161) at the point of relapse. In their preferred model structure, the ERG assumed the management cost for the relapsed health state to be zero.

We understand the concern expressed by the ERG due to the model structure not being able to capture the proportion of patients that may reach CR2 following successful subsequent therapy. We therefore recognise that assuming a cost of £4,884 per cycle for the relapsed health state may be an overestimate.

However, conversely, we believe that assuming a zero management cost for the relapse health state is implausible and is likely to be a significant underestimate as management costs following relapse in first-line can be quite high. Whilst the cost for secondary therapy has been included as a one-off cost (£9,161) at the point of relapse, this cost only covers the administration of one subsequent chemotherapy and does not cover further lines of chemotherapy or the management after first- line. This also does not include the costs of supportive care which can be quite high, as highlighted in Wang et al (2014).

Estimating the cost for the relapse health state in our model is challenging, as this health state includes any subsequent health states following first-line treatment (CR2, relapse, supportive care etc) in people alive who are not in CR1 or who did not receive a transplant. Therefore, to help inform this parameter, data were sought from a previous economic model in AML conducted in the UK and published by Wang et al (2014).[7] This study reported the long-term medical costs associated with AML in the UK based on data from the HMRN database. Medical costs were calculated using a bottom-up costing approach (micro-costing).

Wang et al (2014)[7] reported the cost (2007 values) for different health states (Staying in first relapse, Staying in second relapse, Staying in first remission after month 18, Staying in second remission after month 18) in the first and subsequent months in people with AML who experienced early remission (defined as achieving remission within 50 days) or late remission (defined as achieving remission after 50 days). Costs were also reported during induction for people who achieved or who did not achieve a response.

Monthly costs assumed in Wang et al (2014)[7] in post-remission are summarised below in Table 2 (2007 values). Costs are reported in people aged below 60 years and over 60 years (presented in brackets).

Table 2 Mean cost per month (2007 values) reported in Wang et al (2014)[7] in post-remission (following induction treatment)

	Remission achieved within 50 days		Remission achieved after 50 days	
	Month 1 (£)	**Month 2+ (£)**	**Month 1 (£)**	**Month 2+ (£)**
Staying in first relapse	7,380 (5,002)	1,589 (885)	3,450 (2,562)	1,401 (762)
Staying in second relapse	11,698 (5,002)	5,850 (885)	3,450 (2,562)	1,401 (762)
Staying in first remission after month 18	40 (65)	40 (65)	615 (457)	615 (457)
Staying in second remission after month 18	68 (280)	68 (280)	615 (457)	615 (457)

As expected, costs were greater in the first month and lower in the subsequent months. In the subsequent months (month 2 onwards) in people aged less than 60 years (with early response <50 days), the study reported a cost of £1,589 per cycle (2007 values) in people staying in first relapse, £5,850 per cycle in people staying in second relapse, £40 in people staying in first remission after month 18 and £68 in people staying in second remission after month 18. In people aged less than 60 years (with late response >50 days), the study reported a cost of £1,401 per cycle in people staying in first relapse, £1,401 per cycle in people staying in second relapse, £615 in people staying in first or second remission after month 18.

Whilst it is difficult to map the exact costs from the health states in this study to our relapse health state (as the latter includes a mix a patient who may be in CR2, on supportive care or remain in relapse), we believe this study supports the assumption of a non-zero cost for the relapse health state in our economic model.

Estimating the cost for the relapsed health state in our economic model is challenging and it is difficult to put an exact value to this cost without modelling the whole pathway. However, based on the range of costs reported in Wang et al (2014),[7] we believe that assuming a cost per cycle (28 days) of £2,000

to be a reasonable and possibly a conservative estimate in the absence of alternative robust evidence. This is based on the following considerations. Only partial information was available in Wang et al (2014)[7] and therefore it was not possible to create a robust weighted average. For instance, if we were to assume that 25% of patients had the cost for staying in first relapse (£1,914 uplifted to 2017), 25% of patients had the cost for staying in second relapse (£7,048 uplifted to 2017), 25% of patients had the cost for remission after month 18 (£48 uplifted to 2017) and 25% of patients had the cost for second remission after month 18 (£82 uplifted to 2017), the cost per month for the relapse health state would be £2,273 (or a cost per cycle of £2,091). However, it should be noted that assuming 25% of patients in each of these health state is arbitrary and the proportions could be different. Such an approach also ignores the cost for the first month which is higher, and the cost in people moving to supportive care which can be very high, as suggested in Wang et al (2014).[7]

It should also be noted that a cost of £2,000 per cycle is close to the cost per month reported by Wang et al (2014)[7] after uplifting to 2017 for the health state "staying in first relapse". Whilst we acknowledge that a proportion of patients may move to long-term remission and have lower costs, equally a proportion of patients may move to second or third relapse and experience higher costs as reported by Wang et al (2014).[7] A proportion may also move to supportive care and are likely to experience even greater costs as suggested in Wang et al (2014).[7]

Therefore, despite the uncertainty, we believe that a cost per cycle of £2,000 for the relapse health state represents a more plausible estimate than the zero cost used by the ERG. We believe that based on Wang et al (2014),[7] assuming zero costs for the relapse health state is underestimating the long-term costs. We further believe that the cost per cycle for the relapse health state could be higher, but robust evidence is lacking and therefore a cost of £2,000 per cycle was used in order to provide a reasonable estimate in the absence of robust alternative evidence. We also felt that using a cost per cycle of £2,000 for the relapse health state, supported by evidence, provides a compromise compared with the original cost used for this health state.

Assuming the cost per cycle in the relapsed health state to be £2,000 instead of £0 (as suggested by the ERG) reduces the ICER from £62,712 to £42,869 without PAS.

4.1.4 Updated SMR to reflect the response obtained from 7 UK clinical experts and comments from the clinical experts at the NICE ACM

In our original submission to NICE, we assumed that patients still alive at the end of the trial followed the general population mortality, based on clinical advice. The ERG considered that patients with AML would die at a faster rate compared with the general population and assumed a SMR of 4.

Whilst we understand that the mortality rate in people with AML may be slightly higher compared with general population due to the presence of comorbidities, there is uncertainty regarding the rate at which patients with AML die compared with the general population.

Following clinical advice, an SMR of 4 is likely to be an overestimate. This is supported by the view of the clinical experts during the NICE committee meeting which suggested a SMR of around 2. As mentioned in the ACD, "The clinical experts stated that they would expect mortality risk to increase following stem cell transplant, but that an overall 4-fold increase in mortality rate seemed high".

In order to inform this parameter, we asked 7 UK clinical experts to suggest what SMR they would expect to see in clinical practice in individuals with FLT3 mutation-positive AML compared to the general population. Individual responses are provided below. In brief, clinical experts believed the SMR to range to be between [redacted].

Table 3 Estimates of SMR for individuals with FLT3 mutation-positive AML compared to the general population according to UK clinical experts

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Whilst we understand the value of SMR to be uncertain, this supporting evidence demonstrates that the use of an SMR of 4 is inappropriate and that an SMR of 2 represents a more plausible estimate. It should be noted that an SMR of 2 (as suggested by the clinical experts present at the NICE ACM) may be considered conservative and an overestimate when compared with values suggested by the 7 UK clinical experts.

Assuming an SMR of 2 instead of 4 reduces the ICER from £62,712 to £55,102 without PAS.

4.1.5 Alternative approach to age-adjustment

The ERG considered that utility values should be adjusted by age to reflect the natural variation in utility value by age. Different approaches can be used to age-adjust utility values. The ERG adjusted the utility value in the model for age using the starting age of the model as an anchor.

However, the utility values were sourced from studies that included a generally older population.

Whilst we acknowledge that different approaches exist to adjust utility values by age, we consider that using the mean age of the patients in the different utility studies as an anchor when adjusting utility value by age to be more appropriate and reflective of the true utility values compared with using the starting age in the model.

Using an alternative approach to adjust utility value by age only has a minimal impact on the ICER reducing it from £62,712 to £61,904 without PAS. However, because of the older population included in the utility studies, we feel that such an approach is more appropriate compared with the ERGs approach of using the starting age of the model (45 years) as an anchor.

5 Results

5.1 Revised base-case without the PAS

Incorporation of the changes described above, reduces the ICER from £62,810 to £31,626 prior to implementing the PAS price for midostaurin.

Table 4 Impact of changes in the model on ICER

	Impact of individual changes	Cumulative ICER
ERG base-case	£62,810	-
ERG base-case (correction for inconsistencies)	£62,712	-
SMR = 2	£55,102	£55,102
Utility value for relapse = 0.655 (instead of 0.83)	£55,579	£49,094
Management cost in relapse = £2,000 (instead of £0)	£42,869	£32,107
Method to age-adjust utility value	£61,904	£31,626

5.2 Revised base-case with the PAS

The company offered a confidential PAS [redacted] reducing the midostaurin list price to the NHS.

The ICER using the ERG preferred base-case assumption (prior to correction of the inconsistencies found and changes made by the company following the ACD) after incorporating the PAS was [redacted]

The ICER was further reduced when amending the inconsistencies found and using more appropriate inputs as discussed in section 3. Incorporation of the changes described above, reduces the ICER from [redacted] to [redacted].

Table 5 Impact of changes in the model on ICER with PAS

	Impact of individual changes	Cumulative ICER
ERG base-case	[redacted]	[redacted]
ERG base-case (correction for inconsistencies)	[redacted]	[redacted]
SMR = 2	[redacted]	[redacted]
Utility value for relapse = 0.655 (instead of 0.83)	[redacted]	[redacted]
Management cost in relapse = £2,000 (instead of £0)	[redacted]	[redacted]
Method to age-adjust utility value	[redacted]	[redacted]

5.3 Exploratory analysis

A key source of uncertainty is the cost per cycle for the relapsed health state. In our revised base-case, a cost of £2,000 was used, supported by the range of costs reported in Wang et al (2014).[7] However, as previously highlighted, it is difficult to provide an exact value due to differences in the health states and the fact that costs for all health states were not reported in this study.

Whilst we believe a cost of £2,000 to be possibly conservative, when considering costs reported in Wang et al (2014),[7] this parameter remains uncertain. Therefore, to help inform the committee decision, a threshold analysis was conducted assuming the cost per cycle for the relapse health state to range between £0 (implausible) to £4,500.

ICERs are generated after implementing the PAS, under our revised base-case assumption, assuming a relapse cost per cycle of £2,000, alternative approach to age-adjusted utility, SMR of 2 and utility value for relapsed health state of 0.655.

Figure 1 ICER according to cost per cycle in the relapsed health state, with PAS

As expected the ICER decreases as the cost of relapse increases.

6 Conclusion

Based on the new, additional evidence from the HMRN database, median OS in people newly diagnosed with FLT3 mutation-positive AML is approximately 1 year and hence most people who would be eligible for midostaurin live less than 24 months from diagnosis of FLT3 mutation-positive AML. Thus midostaurin meets the NICE end-of life criteria.

Prior to implementing the PAS price for midostaurin, an ICER of £31,626 per QALY gained is more plausible than the ERG's preferred ICER, based on implementing a more realistic SMR of 2 (based on clinical expert opinion), and more appropriate values for costs and utility in the relapsed health state.

Following implementation of the PAS, the ICER is further reduced from £31,626 to [redacted].

7 References

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Single Technology Appraisal (STA)

Midostaurin for untreated acute myeloid leukaemia [ID894]

ERG commentary on the additional evidence submitted by the company in response to the ACD

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Date	**12/01/2018**

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted], all academic-in-confidence (AIC) data are highlighted in [redacted].

1 Overview

The evidence review group (ERG) was requested by NICE to provide validity checks on the additional evidence submitted by the company in response to the appraisal consultation document (ACD) and to identify any areas of remaining uncertainty. Due to the limited time available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. However, the ERG has checked the implementation of any proposed changes and ensured replication of the results presented by the company.

The company's response to the ACD included:

1 A note on factual inaccuracies in the 1st committee meeting presentation slides;
2 Additional evidence supportive to End of Life;
3 Cost-effectiveness results from an amended version of the ERG's base-case model which includes a revised company base-case.
4 A proposed confidential patient access scheme (PAS) [redacted]
5 Exploratory analysis – a threshold analysis assuming the cost per cycle for the relapse health state to range between £0 to £4,500

The revised model incorporates corrections for minor inconsistencies identified by company and a number of changes to the ERG's base-case analysis which include (a) updated utility value and management costs for the relapsed heath state; (b) a new standardized mortality ratio (SMR); and, (c) an alternative approach to adjust the utility values according to age. Table 1 presents the summary of the changes in the model, a more details are described in the Section 2.3.

Table 1 Summary of the key changes to model

Parameter	Assumption in CS base-case	Assumption in ERG base case	Assumptions in Committee's preferred scenario	Assumption in revised base-case (response to ACD)
CR1L, relapse and post-SCT health state utilities	Health state utilities applied in perpetuity: CR1L 0.83, relapse 0.53 and post-SCT 0.81.	All patients enter cured health state after initial treatment (utility 0.83)	All patients enter cured health state after 3 years (utility 0.83).	Health state utilities applied in perpetuity as per original base-case, relapse utility revised to 0.655.
CR1L, relapse and post-SCT health state costs	Health state costs applied in perpetuity.	Zero health state costs after initial treatment and one of management cost of secondary therapy applied for relapsed patients.	CR1 health state costs applied after 3 years. Zero health state costs applied after cure point (~6.2years).	Health state costs applied in perpetuity; relapse health state costs revised from £4,884 per cycle to £2000 per cycle.
Standardized mortality ratio (SMR)	Mortality same as general population mortality after cure point	4 fold multiplier applied to general population mortality after cure point	4 fold multiplier applied to general population mortality after cure point	2 fold multiplier applied to general population mortality after cure point

Utility adjustment according to age	None	Utility values adjusted according to age using algorithm from Ara and Brazier (2010), using the starting age of the model as an anchor	Utility values adjusted according to age using algorithm from Ara and Brazier (2010), using the starting age of the model as an anchor	Utility values adjusted according to age using algorithm from Ara and Brazier (2010), using the mean (or estimated mean) age in the source study as an anchor
Population Modelled	Mean age: 45 as per RATIFY trial	Mean age: 45 as per RATIFY trial; alternative ages explored in sensitivity analysis	Mean age: 60	Mean age: 45 as per RATIFY trial
Cure point	Cure points of 6.2 years based on the end of the RATIFY trial data.	Cure points of 6.2 years as per company base-case; alternative cure points explored in sensitivity analysis	Uncertainty in cure point noted; company and ERG assumption of 6.2 years is noted as being the most optimistic.	Cure points of 6.2 years based on the end of the RATIFY trial data.

The ERG considers that the documentation submitted in the company's response reflects a number of amendments and corrections intended to address the NICE Appraisal Committee's considerations raised within the ACD and ERG report, but as noted above the company's revised base-case focused on amending the ERG's base-case analysis and not the committee's preferred analysis. The company's revised base-case therefore deviates from the committee's preferred base-case in a number of ways. Importantly, the company's base-case makes does not incorporate the committee's preferences with regards to the model structure and assumes a mean starting age of 45 as opposed to 60. Exploration of the impact of the company's revised assumptions on the ERG's and committee's preferred base-case is explored by the ERG in Section 2.4 and 2.5 respectively.

2 ERG commentary on the additional evidence

2.1 Response to factual inaccuracy mentioned in Section 2 of Company's response to ACD

The ERG can confirm the highlighted error in the NICE slide set and can confirm that the proposed changes presented in Table 1, Section 2 of Company's response to ACD are appropriate. The ERG, however, notes there is a typo in Table 1. The ICER reflecting the impact of the "units of treatment received based on company's original model (discrepancy corrected)" should read £30,904 instead of £39,904 (individual impact on the ICER).

2.2 Review of additional evidence supportive to End of Life

As part the company's response to the ACD, new evidence was provided on the survival of patients with FLT3+ AML. This new evidence was sourced from the Haematological Malignancy Research Network (HMRN) database. The HRMN database is a large regional UK database that collects detailed information about all haematological malignancies diagnosed in the Yorkshire and Humber region. The median survival for pate tins with FLT3+ AML who have received daunorubicin plus cytarabine as an induction chemotherapy was [redacted]. The company argue that this implies that End of Life criteria should be applied in this appraisal.

The ERG considers that the HRMN data to be a reasonable and representative source of OS data for FLT3+ AML patient, but notes a number of substantive weaknesses with the argument put forward by the company:

- The presented figures cite estimates of median overall survival (OS) and not mean OS more typically used to assess the end of life criteria. The ERG notes that mean OS is often substantially longer than median OS in AML. For example, in the RATIFY trial median survival for patients receiving chemotherapy is 26 months whereas mean OS is [redacted] years (Committee base-case assumptions). Mean OS is therefore also likely to be considerably longer than median survival in this cohort; the ERG does not have access to HRMN data-base and therefore can only speculate as to whether mean OS in this cohort exceeds the 2 year end of life threshold, but considers it highly likely.
- While the company state that only patients who received daunorubicin plus cytarabine as an induction chemotherapy were included in the analysis, it is unclear whether this would include patients receiving palliative doses of chemotherapy. Inclusion of this group would likely lead to a significant underestimation of median OS.
- The HRMN data cited by the company includes data that is now 14 years old and there are likely to have been improvements in OS for patients treated with chemotherapy. Median OS of currently treated AML patients is therefore likely to be higher than the [redacted] estimate provided by the company.
- The ERG notes that there is substantial uncertainty in the estimated median OS (95% confidence interval: [redacted]); and also note that the number of patients this estimate is based upon is not reported by the company in their response.

2.3 Review of revised model

2.3.1 Correction of inconsistencies

In response to ACD, the company reported two inconsistencies in the ERG base-case model.

2.3.1.1 Inconsistency 1: Negative proportion of patients in the relapsed health state

The company identified that the proportion of patients in the relapsed health state could become negative when SMR greater than 2 was applied to the model. The reason this occurs relates to the use of a partitioned survival approach and specifically to the extrapolation of OS and complete response (CR) [which uses event-free survival (EFS)], which despite being correlated (the same events are included in OS and EFS) are independently extrapolated. As such, when a standardised mortality rate (SMR) is applied to OS the rate of death becomes larger, but the extrapolation of EFS remains unchanged. This results in their being more patients in the CR1L and post SCT health state than are alive towards the end of the trace and results in negative values being generated for the relapse health state.

In response to ACD, the company corrected the model by extrapolation CR using general population mortality with an SMR applied, i.e. in the same as the OS survival curve is extrapolated. The ERG considers this a reasonable assumption and it addresses the issue with the negative values generated at the end of the trace. The highlighted inconsistency and proposed correction have negligible impact on the estimated ICER.

2.3.1.2 Inconsistency 2: Double counting of QALYs in the relapse health state

The company's ACD response identified that there is an inconsistency in the estimation of QALYs in the relapse health state relating to patients receiving secondary therapy. The company stated that an additional utility value of 0.30 was added to the proportion of patients in secondary therapy in addition to the utility value for relapse which leads to double counting of utility. The ERG acknowledges that this is an inconsistency and agrees with the correction made by company. The highlighted inconsistency and proposed correction have negligible impact on the estimated ICER.

2.3.2 Updated utility value in the relapsed health state

Acknowledging concerns raised by the ERG, the company's ACD response states that the utility value of 0.53 used for relapsed patients may underestimate the health related quality of Life (HRQoL) of these patients, because the model structure does not allow patients who achieve remission on secondary therapy to be distinguished from patients with relapsed/refractory disease. The company, however, considers that the modifications made in the ERG base-case, where a utility value of 0.83 is applied after treatment, are implausible and likely to be overestimate the HRQoL of these patients. This is because whilst some patients receiving subsequent lines of therapy may gain remission, a proportion of patients will either fail to gain remission (refractory disease) or will experience another relapse and have a lower HRQoL. The company also notes that the Leunis et al, 2014[1] study from which the CR1L health state utility values was obtained, reported a separate value of 0.78 for long-term survivors who experienced a relapse following first-line therapy. The company therefore argue that the maximum value that should be applied in the relapsed health state should be 0.78.

To address the stated concerns the company's revised base-case uses an alternative utility value based on the halfway point between 0.78 and 0.53: 0.655. The justification for this choice of value is based on a study[2] of relapsed and refractory patients that shows that approximately 50% of patients receiving second-line therapy achieve remission.

The ERG considers that the company raises a number of valid points. The 0.83 value almost certainly overestimates the HRQoL of patients in the relapsed health state, at least in the short-term. This is for the reasons stated by the company that the relapsed health state will be made up of patients who have achieved second-line remission and those with relapsed/refractory patients. The ERG, however, does not consider the revisions to the utility value applied in the relapsed health state to be an appropriate way to address these issues. As noted in the ERG's report, patients with refractory or relapse disease will only continue to experience relapse or refractory disease for a relatively short duration of time, after which they will either die or achieve remission. Consequently, in the long-term all alive patients in the relapsed health state will be in remission. Application of a utility value that is substantially lower than experienced by patients achieving first-line remission is therefore not justified in the long-term. Importantly, the ERG also notes that the issues raised by the company are less valid in the committee's more optimistic base-case analysis, as this analysis assumes that relapsed patients do not experience the remission utility value for the first three years of the models time horizon. This is because after three years we would expect the vast majority of relapses to have occurred and as such that the vast majority of patients in the relapse health state will be in long-term second-line remission.

With respect to the company's argument that the maximum utility value for relapsed/refractory patients should be no more than 0.78. The ERG considers the company's argument persuasive, though the ERG do note that the utility values for patients achieving first-line and second-line reported in Leunis et al, 2014[1] were not statistically significantly different. The ERG do not, however, consider that application of this utility value will have a substantive impact on the estimated ICER.

2.3.3 Management cost of the relapsed health state

A key concern of the ERG was the company's base-case model assumed substantial ongoing (£4,857 per cycle) health state costs for patients in the relapsed health state. The ERG considered this assumption unreasonable because it does not account properly for remission after relapse and assumes that patients who achieve long-term remission on secondary therapy have substantiality higher health state costs than those who achieve remission on first-line therapy.

The ERG's base-case therefore assumed zero health state costs after first-line treatment was discontinued, but applied one off health state/administration costs (£9,161) for patients experiencing relapsed/refractory disease. The committee considered that these assumptions were too conservative and instead in its preferred analysis assumed that relapse patients enter a cure state with lower health

state costs after 3 years and that beyond the cure point of 6.2 year patients would not incur any further health state costs.

In their response to the ACD the company states that they consider the assumption of zero cost for relapsed patients (either after initial therapy or the cure point) unrealistic and presents alternative analysis reinstating these costs. In this analysis the company revises the health state costs incurred by relapsed patients from £4,857 in the original company base-case to £2000 per cycle. As in the company's original base-case analysis costs are incurred until death. The revised health state costs are based on evidence from a previous UK economic model in AML published by Wang et al (2014).[3] This study reports the long-term costs associated with AML in the UK, with medical costs calculated using a bottom-up costing approach (micro-costing). In deriving the £2000 figure the company notes the difficulty of applying an appropriate health state cost as the model structure adopted does not distinguish between patients who have achieve complete response on secondary therapy and those with relapsed or refractory disease. The company also notes that the £2000 figure adopted does not include costs associated with the transition to supportive care which they highlight as likely to be substantial. Acknowledging this uncertainty, the company implements a threshold analysis exploring the impact of varying the relapse health state costs applied.

The ERG considers the Wang[3] study to be a useful source of cost data for patients with AML, but notes some limitations with the data available. Principally, the ERG notes that the study has limited follow up; maximum follow up is 6 years with only small numbers patients followed up beyond 3 years. Indeed, the paper states that some parameters of the life time model need further refinement because only a few patients survived beyond 5 years in the source data. Further it states that this "might have an impact on the accuracy of the model predictions". It is therefore not clear how appropriate it is to extrapolate the figures obtained from the Wang[3] study over a lifetime time horizon. This is important as the company's approach seeks to rebut the assumption made in both the ERG's and committee's base-case that the long-term management and monitoring costs for AML patients will be zero.

Further to the above, the ERG also has number of substantive concerns regarding the approach taken by the company.

Central to the ERG original critique of the company's model was that it was not clear that patients in the relapse health state would continue to incur substantial management and monitoring costs in perpetuity. The company's revised base-case while using a lower figure still retains this assumption. The inconsistency in this approach is highlighted in the company's derivation of the £2000 per cycle figure month as it assumes that 50% of patients are in first/second remission (25% in each) and 50% are in first/second relapse (25% in each). This is reasonable in the short term, but in the long-term all

alive patients will be in remission. It therefore does not make sense to apply health state costs associated with relapsed/refractory disease in the long-term.

The ERG also considers the approach taken by the company in the application of heath state costs to the relapse health state cost is inconsistent as it assumes that only patients who achieve remission on secondary therapy incur monitoring and management costs, while patients who achieve remission on first-line do not incur any health state costs (after treatment). This is both inconsistent with the committees preferred scenario which assumes ongoing health state costs for all patients up to the cure point and the Wang[3] study which reports non-zero health state costs for patients who achieve first-line remission.

Given these substantive weakness the ERG does not consider the new analysis presented by the company with respect to the relapse health state costs to be a plausible scenario. Further, because the issues raised relate to the model structure adopted, the ERG does not consider the exploratory threshold analysis presented by the company to be an informative exploration of the impact of this parameter.

2.3.4 Updated SMR

The ERG's base-case analysis assumed that following the cure point (~6.2 years) patients would experience a 4 fold increase in mortality over the general population. This figure was estimated based on a long-term follow-up study of patients who have received Hematopoietic Stem Cell Transplantation (HSCT).[4]

The company, noting concerns raised by clinical experts at the NICE committee meeting, consulted with 7 UK clinical experts and elicited clinical opinion on the likely elevated mortality risk experienced by FLT3 mutation-positive AML patients. The SMRs elicited ranged from [redacted]. This was used to justify the company's revised assumption of applying a SMR of 2 inline with comments made by the clinical experts present at the NICE committee meeting.

The ERG, accepts that there is a degree of uncertainty in the long-term mortality of FLT3+ AML patients and as noted in our report the 4 fold multiply applied in the ERG base-case model was based on estimates derived from historic cohorts and hence may over-estimate mortality, compared with current practice. The ERG also acknowledges that these studies focus on the long-term survival of AML patients, following SCT, and that the long-term survival of patients achieving remission with drug therapy alone may be different. The ERG, however, raises two points with regards to the SMR applied in the company's revised base-case. Firstly, the ERG note that the ERG used the most optimistic value from the available literature and that a number of other studies reported higher SMRs (Range 4 to 19.2).[4-6] The values elicited from the clinical experts are therefore considerably more

optimistic than those estimated in the published literature. Secondly, the company's alternative SMR is based on clinical opinion; no actual data in support of the alternative SMR of 2 is presented. The ERG recognises that the company has sought the opinion of a relatively large number of clinicians all of which estimate the SMR to be lower than 2, but this must be weighed against actual data on the relative mortality of AML patients compared with the general population. On this point the ERG notes that conceptually an SMR is a very difficult concept to guesstimate; estimation of an SMR requires both extensive follow up and requires a clinician to make comparisons to external group (the general population) who the clinician may not have direct professional experience of treating. The ERG therefore consider that the while the weight of clinical opinion seems to favour a lower SMR, the inherent issues of eliciting such a value make these estimated values inherently unreliable and as such considers that the values published in the literature are a more reliable source of data on the long-term mortality risks of AML patients.

2.3.5 Alternative approach to age related utility

The company's response to the ACD presents an alternative approach to age-adjustment utility values. This revisions uses the mean (or estimated mean) age in the source study as an anchor rather than the mean age of the modelled cohort (45 years) which is used in the ERG's approach. Where the mean age of the population is not available the mean age of the modelled cohort is used.

This approach has the advantage over the ERG's approach that accounts for the fact that the source utilities were obtained from older cohorts and therefore accounts for the fact these values may not be generalizable to a younger cohort. The company's revised approach also has a number of disadvantages. Firstly, it adds considerable additional computation complexity. Secondly, the application of this approach means that different age adjustments are applied for different utility values which could be argued is inconsistent. For example, mean age of 69 years is used for utility values for induction treatment, while a mean age of 60 is used to adjust utility value for consolidation and maintenance treatment. The age related utility decrement starts after 69 years for people in induction treatment and 60 years for consolidation and maintenance treatment. Given the relative advantages and disadvantage and the marginal impact of the company's alternative approach the ERG is indifferent as to the method used to estimate the age adjusted utilities.

2.4 Review of revised base-case

The impact of incorporating the company's revised assumption into the ERG's base-case is presented in Table 2. The cumulative impact of these alternative assumptions is reduce the ICER from £62,810 ([redacted]) to £31,626 ([redacted]).

Table 2 Impact of changes in the model on ICER

	Without PAS		With PAS	
	Impact of individual changes	**Cumulative ICER**	**Impact of individual changes**	**Cumulative ICER**
ERG base-case	***£62,810***	-	[redacted]	-
ERG base-case (correction for inconsistencies)	£62,712	-	[redacted]	-
SMR = 2	£55,102	£55,102		
Utility value for relapse = 0.655 (instead of 0.83)	£55,579	£49,094		
Management cost in relapse = £2,000 (instead of £0)	£42,869	£32,107		
Method to age-adjust utility value	£61,904	£31,626		
Company's base-case (including corrections and changes)	***£31,626***	-	[redacted]	-

2.5 Review of revised base-case assumptions on the Committee's preferred analysis

As noted in Section 2.2, the committee's base-case differed somewhat from the ERG's preferred analysis and specifically it assumed the following:

- That all alive patients transition to the cure health state after 3 years, and
- That all patients incur zero health sate costs after the cure point.
- A mean starting age of 60.

Table 3 presents additional analysis carried out by the ERG incorporating the company's new assumption into the committee's preferred analysis. The cumulative impact of these alternative assumptions is reduce the ICER from £62,818 ([redacted]) to £56,749 ([redacted]). Note modification of the company's revised model was required to incorporate both the change to the starting age and the alternative method of age adjusting the utilities. Specifically, the ERG have only applied the age adjustment when the alternative anchor proposed by the company exceeded the starting age of 60. This mean that the alternative method proposed by the company only effects the utility value used in the induction health state. In all other respects the age adjustment applied is the same as in the ERG/committee base-case.

Table 3 Impact of changes in the model on ICER

	Without PAS		With PAS	
	Impact of individual changes	**Cumulative ICER**	**Impact of individual changes**	**Cumulative ICER**
Committee base-case	£62,818	-	[redacted]	-
Committee base-case (correction for inconsistencies)	£63,488	-	[redacted]	-
SMR = 2	£53,695	£54,148	[redacted]	[redacted]
Utility value for relapse = 0.655 (instead of 0.83)	£62,083	£52,126		
Management cost in relapse = £2,000 (instead of £0)	£70,427	£56,740	[redacted]	[redacted]
Method to age-adjust utility value	£64,130	£56,749	[redacted]	
Company's base-case (including corrections and changes)	***£56,749***	-	[redacted]	-

The impact of the company's revised assumptions on the committee's base-case is somewhat different to when they applied to the ERG's base-case. In particular, the application of the company's revised relapsed health state costs act to increase the ICER when applied to the committee's base-case where they act to reduce the ICER when applied to the ERG's base-case. The reason for this difference is that in the committee's base-case substantial incremental costs are accrued by patients in the relapsed health state, which are not accrued in the ERG's base-case. The application of the company's revised health state costs reduces the magnitude of these incremental costs relative to the committee's base case while increasing them relative to the ERG's base-case.

3 Conclusion

The company's response to the ACD included additional evidence supportive to End of Life, a proposed PAS and a revised economic model.

The new evidence in support of End of Life provided real world evidence on the median OS survival FLT3+ AML patients. The ERG considers the real world evidence used to be reasonable (subject to a number of caveats), but noted that the newly presented data was on median OS, not mean OS more typically used to assess End of Life criteria. The ERG considers that it is highly likely that mean OS of FLT3+ AML patients exceeds 2 years.

The revised model makes a number of amendments and corrections intended to address the committee's considerations and points raised in the ERG report. The revisions to the ERG base-case included:

- Application of an updated utility value in the relapse health state;
- Application of an updated health state costs in the relapsed heath state;
- Application of a revised standardized mortality ratio (SMR);

- Application of an alternative approach to adjust the utility values according to age.

The ERG considers that a number of the changes made by the company are not well justified and fail to address concerns raised by both the ERG and committee relating to the model structure adopted. The partial exception to this being the alternative method for adjusting utility values, though this has minimal impact on the ICER. The ERG also noted that the revisions made by the company were applied to the ERG's base-case rather than to the committee's preferred analysis. The ERG therefore carried out additional scenario analysis to assess the impact of the company's revised assumptions on the committee's preferred analysis. The impact of the revised assumptions is to lower the ICER from £62,818 ([redacted]) to £56,749 ([redacted]).

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Response to FAD – Midostaurin for untreated acute myeloid leukaemia [ID894]

Dear Meindert,

The base-case ICER calculated by the ERG and considered at the 2nd appraisal committee meeting on 23rd January was £56,749 per QALY gained without a PAS. This was reduced to £[redacted] with the [redacted]PAS discount applicable at that time.

Based on the FAD, we understand that the Committee's preferred assumptions are as follows:

a) Surviving patients with relapsed disease enter a cured health state after 3 years;
b) Management costs of £2,000/cycle should apply for the relapsed health state;
c) The original Novartis calculation for time on treatment should apply
d) Novartis' new approach for adjusting utility should apply
e) Costs for AEs associated with SCT should be included in the model
f) A trial (RATIFY) based economic model should be used
g) A twofold increase in mortality after the cure point is plausible but is associated with uncertainty;
h) The Committee concluded that the lower mean age from the HMRN database is plausible
i) A utility value of 0.78 should apply for the relapsed health state

The ICER of £56,749 was based on the Committee's preferred assumptions a) to g) inclusive (as described above).

In order to assess the impact of the remaining preferred assumptions we explored the impact of:

- Changing the utility value of the relapse health state from 0.655 to 0.78;
- Changing the mean age from 60 years to [redacted] (based on data from the HMRN);

In addition, scenarios are presented exploring some of the uncertainty regarding standard mortality rate and cure point as follows:

- Changing mortality after cure point from twofold to fourfold and;
- Exploring the impact of cure point at either 4 (50 cycles) or 7 (91 cycles) years instead of 6.2 (81 cycles) years

The version of the economic model used by the ERG to generate the £ 56,749 ICER without PAS (received by us on 19th January) was used to update the PAS and explore the assumptions and uncertainties described above. We have therefore not attached a copy of the model (as it is the same version as the ERG used previously) but we are very happy to provide it if this is helpful. Results from the exploratory analyses showing individual and cumulative impacts on the ICER are presented in Table 1 below.

Table 1: ICERs resulting from individual and cumulative changes with and without the PAS

	ICER without PAS	ICER With PAS ([redacted] discount)
	Individual change	Individual change
Base* with committee's preferred/plausible assumptions	**£56,749**	[redacted]
1) Mean age = [redacted]	£44,585	[redacted]
2) Utility value = 0.78	£62,201	[redacted]
Base* + 1) + 2)		[redacted]
Base ** with exploratory scenarios		
3) SMR = 4	£68,881	[redacted]
Base** + 1) + 2) + 3)		[redacted]
4) Cure point after 50 cycles	£54,799	[redacted]
Base** + 1) +2) +3) +4)		[redacted]
5) Cure point after 91 cycles	£59,711	[redacted]
Base** + 1) +2) +3) +5)		[redacted]

* Uses Committee's preferred assumptions a) to g) shown above

** Uses Committee's preferred assumptions a) to h) shown above

Increasing the level of PAS discount to [redacted] reduces the base case ICER from £56,749 to £[redacted] per QALY gained. Exploratory analyses to evaluate the impacts of applying different assumptions in the model both individually and cumulatively are presented in Table 1. When the Committee's preferred/plausible assumptions regarding relapse utility and mean age are considered together, the cumulative impact results in an ICER of [redacted] with PAS. When these assumptions are combined with a more conservative fourfold standard mortality rate the ICER increases to [redacted] with PAS. When a cure point of 50 cycles is applied together with the aforementioned changes the ICER is [redacted] with PAS whereas if a cure point of 91 cycles is used the ICER is [redacted] with PAS. When considering the impact of the Committee's preferred/plausible assumptions and exploring some of the areas of uncertainty, the exploratory analyses demonstrate that, with the improved PAS, the ICER remained within acceptable limits ranging from the ICER [redacted] to [redacted].

Please do not hesitate to contact me if you wish to discuss anything or require any further clarification or analysis.

Regards,

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Single Technology Appraisal (STA)

Midostaurin for untreated acute myeloid leukaemia [ID894]

ERG commentary on the additional evidence submitted by the company in response to the FAD

Produced by	**CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD**
Date	**15/03/2018**

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

1 Overview

The evidence review group (ERG) was requested by NICE to provide validity checks on the additional evidence submitted by the company in response to the final appraisal (ACD).

The company's response to the FAD included:

1 A revised confidential patient access scheme (PAS) [redacted];
2 Cost-effectiveness results using the Committee's preferred assumptions;
3 Exploratory analysis – exploring a number of assumptions considered plausible by the committee.

The ERG considers that the documentation submitted in the company's response largely reflects amendments and alternative assumptions intended to address the NICE Appraisal Committee's considerations raised within the FAD.

2 Revised Patient Access Scheme (PAS)

The company has proposed a revised PAS which is now incorporated into a revised base-case. The PAS consists of a [redacted] midostaurin. This is an increase from the original PAS of [redacted].

The impact of the revised PAS is to reduce the ICER from £56,749 to [redacted]. The ERG has checked the revised economic model and is satisfied that the revised PAS has been correctly implemented by the company.

3 ERG commentary on the additional Scenario analysis

The company also presents additional scenario analysis exploring a number of alternative assumptions, namely:

- A mean chort age of [redacted] based on HMRN data;
- A utility value of 0.78 for relapsed patients;
- Alternative post cure standardised mortality rate (SMR) of 4;
- Alternative cure points of 50 cycles and 91 cycles.

A summary of the results of the additional scenario analysis is presented in Table 1.

Table 1: ICERs resulting from individual and cumulative changes with and without the PAS

	ICER without PAS	**ICER With PAS (discount)**
Base with committee's preferred assumptions	**£56,749**	
1) Mean age = , (60 in base-case)	£44,585	
2) Relapsed utility value = 0.78 (0.655 in base-case)	£62,201	
Base + 1) + 2)		
3) SMR = 4	£68,881	
Base + 1) + 2) + 3)		
4) Cure point after 50 cycles	£54,799	
Base+ 1) +2) +3) +4)		
5) Cure point after 91 cycles	£59,711	
Base + 1) +2) +3) +5)		

The ERG has checked the revised economic model and is satisfied that the additional analysis presented by the company has been correctly implemented by the company. For clarification purposes the ERG wishes to make it clear that cumulative scenarios presented by the company included the assumption that the relapsed health state utility was equal to 0.78, as the company's response is not fully clear on this point.